I. SUMMARY OF THE CLAIMS

Claims 22-24 were cancelled, without prejudice or disclaimer thereof, in response to the Examiner's restriction requirement. Applicants reserve the right to prosecute the subject matter of these claims in this or another application.

In addition, claims 1, 2, 9, 13, 15, 16, 18, 19, 21, 30, 31, 34, and 35 were amended. Claims 1, 2, 9, 13, 15, 16, 18, 19, 30, 31, 34, and 35 were amended to change the term "agent" to "nanoparticulate drug." Applicants define the term "nanoparticulate drug" to encompass all active agents, such as pharmaceutical agents, diagnostic agents, etc. *See e.g.*, page 10, line 24, through page 12, line 17, of the application. Accordingly, this amendment does not narrow the scope of the claims.

In addition, claims 1, 2, 30, 31, and 35 were amended to define the phrase "effective average particle size" as the size at which at least 50% of the drug particles of the composition have a size below the recited amount, as measure by light scattering techniques. *See* page 14, lines 12-14, of the application.

Claims 1, 30, and 35 were amended to change the phrase "2 to 24 hours or longer" to "2 to 24 hours." This amendment was made for the sole purpose of advancing the prosecution of this application.

Finally, claim 36 was added to the application. This claim recites the subject matter of claims 2 and 31, and is dependent upon claim 35.

It is acknowledged that the foregoing amendments are submitted after final rejection of the claims. However, because the amendments do not introduce new matter, and they place the application in better condition for allowance or in better condition for appeal, entry thereof by the Examiner is respectfully requested.

II. SUMMARY OF THE CLAIMED INVENTION

The claimed invention is directed to the surprising discovery of solid dose controlled release nanoparticulate compositions. The controlled release compositions

provide for the therapeutically effective release of an incorporated active agent in a patient for a time period ranging from about 2 to about 24 hours. This discovery was surprising as nanoparticulate compositions are designed for immediate, fast release. Such fast release is a result of the nanoparticulate size of the drug, having a large surface area in relation to the volume, which results in rapid dissolution of the drug following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants unexpectedly discovered that nanoparticulate compositions could effectively be formulated into controlled release formulations. This is not shown or suggested by the cited prior art.

III. THE OFFICE ACTION

Claims 1-22 and 25-35 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,684 ("Liversidge et al."). Office Action at pages 3-5. Applicants respectfully traverse this ground for rejection.

A. Summary of Liversidge et al.

Applicants' claimed invention is an improvement over commonly-owned Liversidge et al., which is the first patent to disclose nanoparticulate drug compositions. *See* page 5, lines 25-27, of the application. Liversidge et al. teach nanoparticulate compositions comprising active agents and surface stabilizers. This reference does not teach incorporation of such nanoparticulate compositions into a controlled release dosage form, as discussed below.

B. Examiner's Basis for the Rejection of the Claims over Liversidge et al.

In support of the rejection, the Examiner stated that Liversidge et al. teach nanoparticulate compositions, excipients for such compositions, and solid dose forms of such compositions. The Examiner then concluded that "[o]ne of ordinary skill in the art would have been motivated to produce a well known pharmaceutical dosage form, such

as a tablet, which incorporates Liversidge's nanoparticles, and the necessary excipients, especially based on Liversidge's disclosure that his particles are intended for this exact purpose." Office Action at page 5. Applicants respectfully disagree with the Examiner's analysis and conclusion.

C. Liversidge et al. Do Not Teach or Suggest Nanoparticulate Controlled Release Formulations

The Examiner appears to be using the terms "tablet" and "solid dose form" to be equivalent to a controlled release formulation. This is incorrect. While formulation of a nanoparticulate dispersion into a tablet may be conventional, formulation of such a dispersion into a controlled release formulation is **not** taught or suggested by Liversidge et al. This is because

> [s]uccessful fabrication of sustained-release products is usually difficult and involves consideration of the physical-chemical properties of the drug, pharmaco-kinetic behavior of the drug, route of administration, disease state to be treated and, most importantly, placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug.

See Chang et al., "Sustained Drug Release From Tablets and Particles Through Coating," Lieberman et al., eds., *Pharmaceutical Dosage Forms: Tablets*, Vol. 3, pp. 199-302, 199 (Marcel Dekker, Inc., New York) (EXHIBIT 1).

Thus, formulation of nanoparticulate compositions into solid dose forms does not teach or suggest the formulation of nanoparticulate compositions into solid dose *controlled release* dosage forms, such as that claimed by Applicants. This is further supported by Chang et al., where they state that "[d]esign of a sustained-release product is normally a very difficult task . . ." Chang et al. at 201. In addition, this reference teaches that drugs with low water solubility, which are encompassed by Applicants' claims, are "difficult to incorporate into a sustained-release mechanism." Chang et al. at 206. This normally difficult task is complicated in the case of the present invention, in which the active agent is in the form of nanoparticles which are designed for *fast* and *immediate* release.

For at least these reasons, Liversidge et al. do not teach or suggest the claimed invention and, therefore, withdrawal of this ground for rejection is respectfully requested.

IV. CONCLUSION

Applicants courteously request reconsideration of this application in view of the above remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: Sept 10, 2001

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Marked-Up Version to Show Changes

1. (Amended) A controlled release nanoparticulate composition comprising:

(a) a poorly soluble nanoparticulate drug [agent] to be administered having an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have an average particle size of less than about 1000 nm when measured by light scattering techniques;

(b) at least one surface stabilizer associated with the surface of the nanoparticulate drug [agent], and

(c) at least one pharmaceutically acceptable rate-controlling polymer,

wherein the composition provides controlled release of the nanoparticulate drug [agent] for a time period ranging from about 2 to about 24 hours[or longer].

2. (Amended) The composition of claim 1, wherein the effective average particle size of the nanoparticulate drug [agent] is selected from the group consisting of less than about 800 nm, less than about 600 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm, wherein at least 50% of the drug particles have an average particle size of less than about 800, 600, 400, 300, 250, 100, or 50 nm, respectively, when measured by light scattering techniques.

9. (Amended) The composition of claim 1 formed by wet granulation, wherein water is added to the nanoparticulate drug [agent], surface stabilizer, and polymer to form granules prior to forming the solid dose of the controlled release formulation.

13. (Amended) The composition of claim 1, wherein the poorly water soluble nanoparticulate drug [agent] is present in an amount of from about 1 μg to about 800 mg.

15. (Amended) The dosage form of claim 14, wherein the nanoparticulate drug [agent] and at least one auxiliary excipient are compressed into tablet form prior to coating with a rate controlling polymer.

16. (Amended) The dosage form of claim 14, wherein the nanoparticulate drug [agent], the rate controlling polymer and at least one auxiliary excipient are compressed to form a controlled release matrix tablet.

18. (Amended) The dosage form of claim 14, wherein the nanoparticulate drug [agent] and at least one auxiliary excipient are compressed into the form of a multilayer tablet prior to coating with a rate controlling polymer.

19. (Amended) The dosage form of claim 14, wherein the nanoparticulate drug [agent] is dispersed in the rate controlling polymer material and compressed into the form of a multilayer tablet.

21. (Amended) The dosage form according to claim 14, wherein the nanoparticulate drug [agent], at least one auxiliary excipient, and the rate controlling polymer material are combined into a multiparticulate form.

30. (Amended) A method of preparing a solid dose controlled release nanoparticulate formulation comprising:

(a) combining a nanoparticulate composition of [an] a nanoparticulate drug [agent] to be administered and at least one surface stabilizer associated with the surface of the nanoparticulate drug [agent], wherein the composition has an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have an average particle size of less than about 1000 nm when measured by light scattering techniques, and at least one suitable rate-controlling polymer; and

(b) forming a solid dose of the mixture from step (a), wherein the solid dose formulation has a controlled release of the nanoparticulate drug [agent] following administration for a time period ranging from about 2 to about 24 hours[or longer].

31. (Amended) The method of claim 30, wherein the effective average particle size of the nanoparticulate drug [agent] particles is selected from the group consisting of less than about 800 nm, less than about 600 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm , wherein at least 50% of the drug particles have an average particle size of less than about 800, 600, 400, 300, 250, 100, or 50 nm, respectively, when measured by light scattering techniques.

34. (Amended) The method of claim 31, comprising adding water to the nanoparticulate drug [agent], surface stabilizer, and rate-controlling polymer to form granules prior to step (b).

35. (Amended) A method of treating a mammal comprising administering to the mammal an effective amount of a solid dose controlled release nanoparticulate formulation wherein:

(a) the formulation comprises nanoparticulate drug [agent] particles to be administered and at least one surface stabilizer associated with the surface of the nanoparticulate drug [agent], wherein the nanoparticulate drug [agent] particles have an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have an average particle size of less than about 1000 nm when measured by light scattering techniques, and at least one suitable rate-controlling polymer; and

(b) the formulation has a controlled release of the nanoparticulate drug [agent] following administration for a time period ranging from about 2 to about 24 hours[or longer].